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REVIEW ARTICLE

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Diagnosis and treatment of pleural mesothelioma. State of the art 2024

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ABSTRACT

Pleural mesothelioma is a cancer with a low incidence and poor prognosis. Treatment of pleural mesothelioma includes surgery, radiotherapy and systemic treatment — chemotherapy and immunotherapy. Tri-modal therapy, consisting of surgery, chemotherapy and radiotherapy, remains the standard for radical management. The stage of the tumour at the time of diagnosis usually precludes surgical treatment. Recent years have seen significant advances in the treatment of all cancers. The introduction of dual immunotherapy into everyday practice resulted in a breakthrough in the treatment of pleural mesothelioma. Last year, the combination of nivolumab and ipilimumab is also available in Poland for patients with pleural mesothelioma, irrespective of the histological type. This article reviews reports on pleural mesothelioma therapy based on guidelines from global oncology organisations and results of clinical trials conducted over the past several years.

Keywords: pleural mesothelioma, tri-modal therapy, systemic treatment, nivolumab with ipilimumab

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Introduction

Pleural mesothelioma (PM), the most common malignant tumour of the pleura, is a rare disease with a poor prognosis. According to the Central Statistical Office, 307 patients (210 men and 97 women) were diagnosed with PM in 2020. At the same time, 316 deaths from this cause were reported (209 men and 107 women). This represents 0.3% of all malignant tumour cases among men, 0.1% of cases among women, and 0.4% and 0.2% of cancer deaths, respectively [1].

The pathogenesis is predominantly related to asbestos exposure. Asbestos, irrespective of chemical differences and those due to its crystalline structure is a naturally occurring mineral. Crocidolite is considered to be the most carcinogenic. As many as 18% of those working in its extraction died of pleural mesothelioma [2]. Due to its proven harmfulness and impact on the development of mesothelioma, in 1997, the use of asbestos-containing products, which for decades had been commonly used in construction throughout the world, was banned in Poland.

Only a year ago, the European Commission once again called on all European Union (EU) institutions and member states to speed up efforts to make the EU asbestos-free. This means that asbestos use is still a problem, and we will continue to see a similar number of patients diagnosed with pleural mesothelioma for at least another decade.

The latency period of this cancer is on average 30 years [3]. At the time of diagnosis, in most cases, there is a disseminated malignant process. The life expectancy of patients not treated with radical intent is 9 months [3]. There are three pathomorphological types of PM: epithelioid (55%), mixed (30%) and sarcomatoid (15%). The worst prognosis histological type is the sarcomatoid type. The median survival time for patients diagnosed with the epithelioid type is approximately 17 months, while the sarcomatoid type is less than 7 months [4]. In addition to histological type, negative prognostic

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factors include clinical stage, older age, elevated acute phase protein (CRP) values, hyperleukocytosis and poor performance status [5].

The most important genetic mutation that is associated with pleural mesothelioma is a germline mutation in the *BAP1* (BRCA-associated protein 1) suppressor gene. A 2017 study analysed histopathological and cytological findings in 81 patients. Mutations in *BAP1* were present in 58% of histopathological and 59% of cytological samples [6]. Germline mutations are associated with tumour occurrence in younger patients and a better prognosis. The median survival time among patients in whom histopathological specimens were examined was 6 and 11 months for *BAP1* negative and positive patients, respectively. However, there is little likelihood of developing a molecularly targeted drug against *BAP1* due to the numerous mutation variants we find in patients with pleural mesothelioma [7].

Treatment of pleural mesothelioma includes surgery, radiotherapy and systemic treatment — chemotherapy and immunotherapy.

For several years, several clinical trials have been conducted to identify the optimal mesothelioma treatment. Currently, the most hopeful approach is immunotherapy. Qualification for the appropriate treatment method is based on staging according to the TNM system (Tab. 1, 2 [8]).

Treatment

Surgical treatment

The primary method of radical treatment for patients in stage I–IIIa is surgery. There are two main methods: extrapleural pneumonectomy (EPP) and pleurectomy with decortication (PD). Currently, an extended pleurectomy and decortication (EPD) version of the PD procedure is most commonly performed. Due to the unfavourable location and spread of mesothelioma, as well as the extent and complications of the above-mentioned procedures, the effectiveness of surgical treatment is often questioned.

In 2011, the results of the MARS (Mesothelioma and Radical Surgery Trial) study comparing the two surgical methods were published. Ultimately, only 50 of 112 eligible patients took part in the trial. Patients were randomly allocated to two arms — one with EPP (24 patients) and the other with PD (26 patients). The median overall survival (OS) time was 14.4 months for EPP and 19.5 months for PD [hazard ratio (HR) = 1.90; 95% confidence interval (CI) 0.92–3.93; p = 0.082] (Tab. 3 [9]).

Patients were also assessed for quality of life (QoL). Patients undergoing pleurectomy with decortication reported better QoL than patients in the extra pleurectomy

Table 1. TNM classification of pleural mesothelioma [Union for International Cancer Control (UICC) 8th edition]. Staging classification of malignant pleural mesothelioma according to the TNM system (National Comprehensive Cancer Network) [8]

T (tumour), primary tumour	
Tx	No evaluation of primary focus possible
T0	No evidence of primary focus
T1	Tumour confined to the mural pleura with or without involvement of: — visceral pleura — mediastinal pleura — diaphragmatic pleura
T2	Tumour involving each of the pleural surfaces on one side (mural, visceral, mediastinal and diaphragmatic) with at least one of the following features: — infiltration of the diaphragmatic muscle — infiltration of the pulmonary parenchyma
T3	Locally advanced, potentially resectable tumour. Tumour involving all pleural surfaces on one side (mural, visceral, mediastinal and diaphragmatic), with at least one of the following features: — infiltration of the intrathoracic fascia — infiltration of adipose tissue — a single, completely resectable tumour focus extending into the soft tissues of the chest wall — infiltration of the pericardium without exceeding its full thickness
T4	Locally advanced, inoperable tumour. Tumour involving all pleural surfaces on one side (mural, visceral, mediastinal and diaphragmatic) with at least one of the following features: — diffuse or multifocal infiltration of the soft tissues of the chest wall — infiltration of the rib — infiltration through the diaphragm on the peritoneum — infiltration of mediastinal structures — indirect infiltration of the contralateral pleura — infiltration of the spinal column — infiltration of the full thickness of the pericardium — presence of tumour cells in the pericardial fluid — infiltration of the pericardium — infiltration of the myocardium — infiltration of the myocardial plexus — infiltration of the brachial plexus
N (lymph nodes), regional lymph nodes	
Nx	Inability to assess regional lymph nodes
N0	No evidence of metastases in regional lymph nodes
N1	Metastasis in lymph nodes on one side: — bronchopulmonary — hilar or — mediastinal — (including nodes of the internal thoracic chain, peribronchial, pericardial or intercostal)
N2	Mediastinal metastases on the opposite side from the primary tumour and/or to the supraclavicular nodes on the same or opposite side
M (metastases), distant metastases	
M0	No distant metastases
M1	Current distant metastases

Table 2. Staging of malignant pleural mesothelioma according to the TNM system [8]

Staging		T	N	M
I	IA	T1	N0	M0
	IB	T2–3	N0	M0
II		T1–2	N1	M0
III	IIIA	T3	N1	M0
	IIIB	T1–3	N2	M0
IV		T4	N0–2	M0
		Any N	Any T	M1

Table 3. Overall survival (OS). The MARS (Mesothelioma and Radical Surgery) study [9]

OS		EPP	PD
Regardless of the histological type	Median OS [months]	12.8	23
	1-year survival	54.5%	81.9%
	2-year survival	18.2%	49%
	5-year survival	9%	30.1%
Epithelioid type	Median OS [months]	12.8	28.9
	1-year survival	57.1%	91.2%
	2-year survival	28.6%	54%
	5-year survival	14.3%	42%
Sarcoma and mixed type	Median OS [months]	8.8	18.3
	1-year survival	50%	62.3%
	2-year survival	0	38%
	5-year survival	0	9.5%

EPP — extrapleural pneumonectomy; PD — pleurectomy with decortication

arm. Serious adverse events (SAEs) occurred in greater numbers in the first arm (10 cases) compared with the second arm (only 2 cases) [9]. These conclusions were confirmed in a non-randomised, prospective study evaluating and comparing two combination therapy regimens. The first arm included initial (neoadjuvant) chemotherapy, extrapleural pneumonectomy and complementary radiotherapy, while the second arm included pleurectomy with decortication and complementary chemotherapy. The median OS was significantly longer in the PD group at 23 months *vs.* 12.8 months in the other group. The 2-year survival rates were 49 and 18.2%, respectively. The 5-year survival rates were 30.1 and 9.0%, respectively ($p = 0.004$). The study confirmed the validity of triple-modality combination therapy in all patients eligible for radical treatment [10].

This has resulted in surgeons moving away from a more radical approach and opting for an indirect method — extended pleurectomy with decortication (the pericardium and diaphragm are additionally partially removed).

In 2013, the results of a meta-analysis comparing these two surgical treatments for pleural mesothelioma (EPP *vs.* EPD) were published. The results again confirmed the superiority of the second method. The perioperative mortality rate was 6.8 *vs.* 2.9%, respectively, $p = 0.02$. Median overall survival times ranged between 13–29 months for EPD and 12–22 months for extrapleural pneumonectomy [11].

As a consequence of the MARS trial, MARS 2 (The Mesothelioma and Radical Surgery Trial 2) was launched to evaluate the efficacy of chemotherapy alone *vs.* chemotherapy in combination with surgery [12]. In 2023, the results of this trial were presented at the World Conference on Lung Cancer (WCLC) congress. Median OS in the first arm with chemotherapy in combination with surgery was 19.3 months and in the arm with chemotherapy alone 24.8 months. Surgery combined with chemotherapy was associated with worse survival, more adverse events, poorer quality of life and higher costs in patients with resectable pleural mesothelioma

compared with chemotherapy alone [13]. The extent of surgery, as well as the histological type of the tumour, determines a cautious approach to the qualification of patients for surgical treatment. However, it should be noted that several aspects regarding the methodology of the study are questionable such as the lack of magnetic resonance imagining (MRI) for initial assessment of disease progression. The lack of uniform imaging modalities raises concerns about the balance in patient selection between the two study arms and the potential impact on outcomes.

The National Comprehensive Cancer Network (NCCN) guidelines recommend surgical treatment only in epithelioid type [14, 15]. Another study conducted in the United States compared patients with mixed and sarcomatoid type at stages I–II (T1–2; N0; M0) treated surgically with those who received chemotherapy/radiotherapy. Surgical treatment prolonged median OS from 4.21 to 7.56 months ($p < 0.01$) in the sarcoma type and from 9.3 to 15.8 months ($p < 0.01$) in the mixed type [16].

In palliative treatment, surgery is used to treat pleural effusion, which is a common manifestation of pleural mesothelioma. For many years, talc pleurodesis has been the standard of care. The superiority of this method was confirmed in the MesoVATS study, which compared two methods of palliative treatment: video-assisted thoracoscopic partial pleurectomy (VAT-PP) *vs.* talc pleurodesis. Talc pleurodesis was performed in 88 patients and VAT-PP in 87. The 1-year survival rate in the former group was 57% (46–66) and in the latter 52% (95% CI 41–62). Operative complications were significantly more frequent after VAT-PP, (31%) than after the second method (14%). In addition, the median hospitalisation time was longer in patients treated with VAT-PP (7 *vs.* 3 days) ($p < 0.0001$) [17, 18].

Radiotherapy

In pleural mesothelioma, radiotherapy is used as a palliative treatment and as part of a complex radical treatment together with surgery and chemotherapy. For several years, clinical trials have been conducted to optimise recommendations by changing methods, doses or the timing of radiotherapy. In 2016, the results of the IMPRINT trial were published, for which patients receiving triple therapy were eligible. Treatment included surgery, chemotherapy and radiotherapy using the intensity modulated radiation therapy (IMRT) technique, which was an innovative method of radiotherapy at the time. The primary endpoint was the number of patients who developed severe pneumonia greater than or equal to grade 3. Twenty-seven of the 45 patients received radiotherapy. Of these patients, 6 patients had grade 2 pneumonia, and two patients had grade 3 pneumonia. None had more serious complications [19]. This study demonstrated the good tolerability of this method of radiotherapy and introduced it as a standard in complex treatment.

In 2005, patients in Switzerland, Belgium and Germany began to be recruited for the SAKK17/04 trial, which aimed to evaluate the efficacy of postoperative radiotherapy. Patients received initial chemotherapy, followed by extrapleural pneumonectomy, which was the standard of care at the time. Patients who achieved complete macroscopic resection were allocated to two groups: patients who would or would not receive radiotherapy. The primary endpoint was relapse-free survival (RFS) — time to recurrence. Only 54 patients (27 in each group) of 151 eligible for chemotherapy participated in the final phase of the study. The median time to local recurrence was 7.6 months (95% CI 4.5–10.7) in the group without radiotherapy and 9.4 months in the group with radiotherapy [20].

Prophylactic radiotherapy in surgically treated patients without the presence of regional or distant metastases

In 2016, the results of the SMART trial were published, which showed no significant difference between the use of prophylactic radiotherapy and radiation at the time of metastasis [21].

A second study evaluating prophylactic radiotherapy, the Prophylactic Irradiation of Tracts (PIT) trial, assessed the appearance of metastases in thoracic lymph nodes within six months after surgery as a primary endpoint [22]. Six of the 186 participants in the study irradiated prophylactically developed metastases, and 10 of the 189 participants in the second arm also developed metastases. After 12 months of follow-up, there was no difference between the 2 arms (15 *vs.* 19 patients) [23]. Current European Society for Medical Oncology (ESMO) recommendations do not recommend the routine use of prophylactic radiotherapy in PM [24].

In palliative treatment, radiotherapy is used when symptoms that arise cannot be controlled with pharmacotherapy. These are mainly pain (in 77%) [24], as well as superior vena cava syndrome, spinal cord compression, bleeding, cough, dyspnoea or risk of bone fracture.

Systemic treatment

Systemic treatment remains the predominant form of treatment for pleural mesothelioma (Fig. 1). Due to their stage, histopathological diagnosis, patient age, concomitant diseases or general condition, patients are often disqualified from surgical treatment. The standard chemotherapy regimen used for many years for pleural mesothelioma has been pemetrexed in

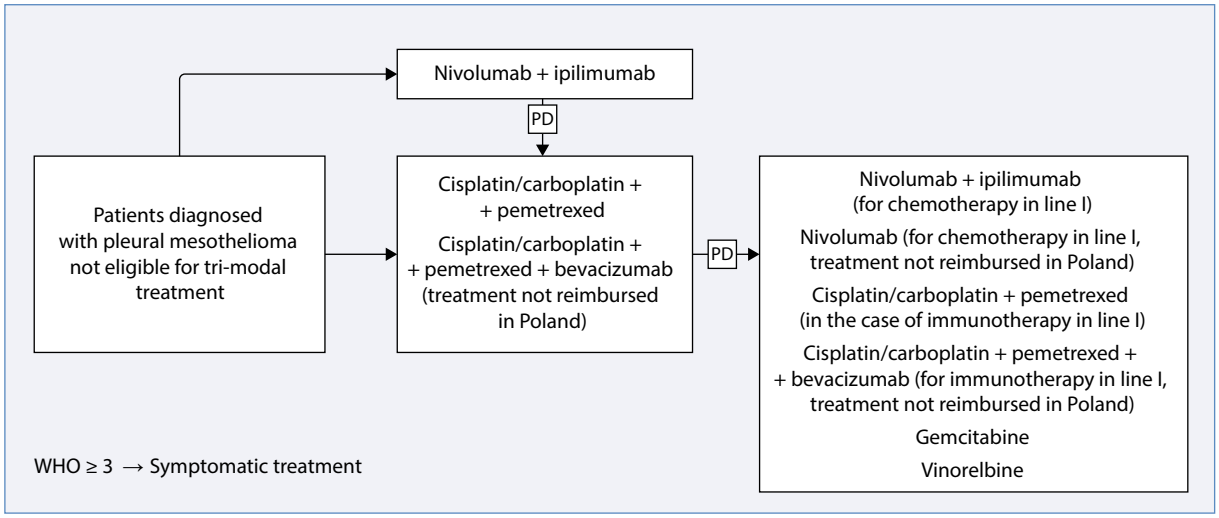

Figure 1. Algorithm of management in the case of inoperable pleural mesothelioma. Based on the European Society for Medical Oncology (ESMO) guidelines (2021); PD — progressive disease; WHO — World Health Organization

Table 4. Characteristics of patients randomised to the two arms of the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) [26]

Total number of patients — 448	**Cisplatin + pemetrexed + bevacizumab; n = 223)**	**Cisplatin + pemetrexed; n = 225**
OS [months]; in brackets — range	18.8 (15.9–22.6)	16.1 (14–17.9)
Grade 3–4 adverse effects (%)	158 (71)	139 (62)
Patient characteristics		
Gender		
Female (%)	55 (25)	55 (25)
Male (%)	168 (75)	170 (76)
Median age	65.7 (61.5–70)	65.6 (60.8–70.3)
Histological type		
Epithelioid (%)	179 (80)	182 (81)
Sarcomatoid + mixed (%)	44 (20)	43 (15)
ECOG		
0–1	125 (56)	129 (57)
2	7 (3)	8 (4)

ECOG — Eastern Cooperative Oncology Group; OS — overall survival

combination with a platinum derivative. The results of a study comparing cisplatin monotherapy with a combination of platinum and pemetrexed were published in 2003. The median survival time was 12.1 months in the pemetrexed arm and 9.3 months in the control arm (HR = 0.77; p = 0.020). The median time to progression was 5.7 and 3.9 months, respectively (p = 0.001). The response rate was 41.3% in the two-drug chemotherapy and 16.7% in the control arm (p < 0.0001) [25].

In 2008, recruitment was opened for a trial that included an anti-angiogenic drug, bevacizumab, in addition to chemotherapy. The study enrolled 446 patients, who were assigned to two arms. Arm one received standard chemotherapy and bevacizumab, while arm 2 received chemotherapy alone. Median survival time was significantly longer in the bevacizumab arm (18.8 *vs.* 16.1 months; p = 0.0167). Grade 3–4 complications were reported in 158 (71%) of 222 patients who received bevacizumab and 139 (62%) of 224 patients who did not [26] (Tab. 4).

Hypertension grade 3 or higher was reported in 51 (23%) of 222 patients treated with chemotherapy and bevacizumab *vs.* 0% in patients receiving chemotherapy alone. Thrombotic complications were found

Table 5. Adverse effects. Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) [26]

Adverse effects	Cisplatin + pemetrexed + bevacizumab		Cisplatin + pemetrexed	
	Total (%)	Severity grade ≥ 3 (%)	Total (%)	Severity grade ≥ 3 (%)
Neutropenia	173 (77.9)	98 (44.1)	177 (79)	100 (44.6)
Anaemia	163 (73.4)	16 (7.2)	187 (83.5)	30 (13.4)
Nausea, vomiting	174 (78.4)	18 (8.1)	172 (76.8)	18 (8)
Hypertension	125 (56.3)	51 (23)	3 (1.3)	0
Cardiovascular complications	137 (61.7)	64 (28.8)	6 (2.7)	2 (0.9)
Haemorrhagic complications	91 (41)	2 (0.9)	16 (7.1)	0
Thrombotic complications	16 (7.2)	13 (5.8)	3 (1.3)	2 (0.9)

in 13 (6%) of 222 patients *vs.* 2 (1%) of 224 patients, respectively [26] (Tab. 5).

European Society for Medical Oncology and NCCN guidelines recommend three-drug chemotherapy as the most effective treatment despite the high risk of side effects. In Poland, bevacizumab is not reimbursed for the treatment of pleural mesothelioma.

In 2019, the results of the LUME-Mes study were published. This was a double-blind, phase II/III study evaluating the efficacy and safety of nintedanib (a tyrosine kinase inhibitor that blocks the activity of VEGFR1-3, PDGFR α and β, FGFR 1) with pemetrexed- and cisplatin-based chemotherapy in first-line treatment in patients with inoperable pleural mesothelioma. The median duration of treatment was 5.3 months (2.8–7.3) in the nintedanib group and 5.1 months (2.7–7.8) in the placebo group. Progression-free survival (PFS) did not differ between the nintedanib group (median 6.8 months) and the placebo group (7.0 months). The primary endpoint for PFS in the phase III LUME-Meso trial was not met. The addition of nintedanib to pemetrexed and cisplatin did not improve disease PFS and thus the phase 2 results were not confirmed [27].

A significant breakthrough in the treatment of pleural mesothelioma was possible thanks to the CheckMate 743 study. The study used two monoclonal antibodies, nivolumab [an antibody directed against the programmed death type 1 receptor (PD-1)] and ipilimumab (an antibody directed against the CTLA-4 antigen). The study regimens compared dual immunotherapy (nivolumab 3 mg/kg intravenously every 3 weeks with ipilimumab 1 mg/kg intravenously every 6 weeks) against chemotherapy [pemetrexed 500 mg/m^2 intravenously with either cisplatin 75 mg/m^2 intravenously or carboplatin for an area under the free carboplatin plasma concentration *versus* time curve (AUC) of 5]. The primary endpoint in the study was median overall survival. A significant difference in favour of immunotherapy was shown. Median OS was 18.1 *vs.* 14.1 months (reduction in the risk of death by 26%; p = 0.0020), respectively. The 2-year survival rate was 41 *vs.* 27%, respectively. Treatment benefit was observed in both groups divided by histological type (patients with epithelioid and non-epithelioid type). Median OS was 18.7 months reduction in risk of death by 14% for epithelioid type and 18.1 months (reduction in the risk of death by 54%) for non-epithelioid types. Significant improvements in 1-year and 2-year survival were comparable in both histological subgroups. However, it is noteworthy that patients with sarcomatoid and mixed types had significantly greater improvement with respect to chemotherapy [28, 29] (Tab. 6).

The most common side effects were skin lesions and diarrhoea in the nivolumab and ipilimumab arms and nausea in the chemotherapy arm. The most common serious adverse reactions were inflammatory bowel disease in arm 1 and anaemia in arm 2. Treatment-related grade 3 and 4 adverse effects were observed in 91 (30%) of 300 in arm 1 and 91 (32%) of 284 in arm two patients [29] (Tab. 7).

In 2021, the European Medicines Agency (EMA) approved a combination immunotherapy treatment for pleural mesothelioma. A year earlier, the treatment was approved in the US. In January 2023, the combination was included in the Polish drug programme for the first-line treatment of pleural mesothelioma in patients ineligible for radical treatment regardless of histopathological type. In second-line treatment, nivolumab with ipilimumab can only be found in NCCN recommendations.

In the second and subsequent lines of treatment, there is no obvious choice regarding a specific therapy. In recent years, many studies have been started to expand the indications for pleural mesothelioma among the drugs that have entered routine oncological treatment.

The first study requiring attention is the CONFIRM trial. Patients in this study who had disease progression

Table 6. Median overall survival (OS) according to age, sex, histological type and general condition of the patient. Three-year results from the CheckMate 743 study [29]

Characteristics of the subgroups identified	Median OS	
Nivolumab + ipilimumab (n = 303)	**Chemotherapy (n = 302)**	
All randomised patients (n = 605) Median OS [months]; in brackets — range	18.1 (16.8–21.0)	14.1 (12.4–16.3)
Age		
< 65 (n = 167)	17.2 (13.1–28.0)	13.3 (10.6–18.3)
≥ 65 and < 75 (n = 281)	20.3 (17.3–24.9)	14.5 (11.6–17.4)
≥ 75 (n = 157)	16.9 (11.0–21.8)	15.5 (11.7–19.1)
Sex		
Female (n = 138)	21.2 (15.7–25.9)	18.0 (12.6–23.8)
Male (n = 467)	17.5 (16.2–20.7)	13.7 (11.7–15.5)
Histological type		
Epithelioid (n = 455)	18.2 (16.9–21.9)	16.7 (14.9–20.3)
Sarcomatoid + mixed (n = 150)	18.1 (12.2–22.8)	8.8 (7.4–10.2)
ECOG		
0 (n = 242)	20.7 (17.5–25.9)	19.5 (15.2–22.8)
≥ 1 (n = 363)	17.0 (14.1–20.3)	11.6 (9.0–13.9)

ECOG — Eastern Cooperative Oncology Group

Table 7. Adverse effects. Three-year results of the CheckMate 743 study [29]

Adverse effects in the nivolumab plus ipilimumab arm (n = 300)	**Total, n (%)**	**In grade 3 or 4, n (%)**
Hypothyroidism	34 (11.3)	0
Hyperthyroidism	11 (3.7)	0
Pituitary insufficiency	6 (3.0)	3 (1.0)
Pituitary gland inflammation	12 (4.0)	3 (1.0)
Adrenal insufficiency	7 (2.3)	2 (0.7)
Rash	40 (13.3)	8 (2.7)
Diarrhoea	18 (6.0)	6 (2.0)
Pneumonia	20 (6.7)	6 (2.0)
Hepatitis	18 (6.0)	14 (4.7)
Acute kidney injury	6 (2.0)	5 (1.7)

after conventional 1st-line chemotherapy were randomly allocated to the nivolumab or placebo group. The median time to disease progression was 3.0 months (95% CI 2.8–4.1) in the immunotherapy arm and 1.8 months (1.4–2.6) in the placebo group (HR = 0.67; 95% CI 0.53–0.85; p = 0.0012). Median survival time was 10.2 months in the study arm and 6.9 months (5.0–8.0) in the control arm, respectively (HR = 0.69; 95% CI 0.52–0.91; p = 0.0090). Serious adverse events occurred in 90 (41%) patients receiving nivolumab and in 49 (44%) patients taking placebo [30]. Subsequent studies have confirmed the efficacy of nivolumab monotherapy in the treatment of PM [31, 32].

The KEYNOTE-028 study assessed the efficacy and safety of pembrolizumab [a monoclonal antibody directed against PD-1 (anti-PD-1)] in the treatment of pleural mesothelioma. This was a non-randomised study. The primary endpoint was the safety and tolerability of treatment. Among the study participants, only five patients (of 25 included in the study) reported adverse effects in grades 3. No deaths were reported by the time of assessment [33].

A retrospective study in the Australian population confirmed the beneficial effect of pembrolizumab with good treatment tolerance. Progression free-survival was 4.8, and OS survival was 9.5 months. Only 27% of subjects experienced adverse effects of grade 3 or higher. Patients presenting Eastern Cooperative Oncology Group (ECOG) 0 at baseline with PD-L1 expression equal to or greater than 1% benefited more from treatment [34].

Another promising drug is avelumab. In 2019, the results of a phase I study were released. Twenty patients (38%) had 3 or more lines of treatment (median 2). The confirmed objective response rate (ORR) was 9% including a complete response in 1 patient and a partial response in 4 patients. The median time to progression was 4.1 months. The median survival time was 10.7 months. Grade 3–4 treatment-related adverse events were reported in 5 patients (9%) and immunotherapy-related adverse events were reported in 3 patients (6%). No treatment-related death was reported [35].

In contrast to the data presented above remain the results of the phase III DETERMINE trial evaluating the efficacy of tremelimumab (an antibody directed against the CTLA-4 antigen) in 2nd or 3rd lines treatment of pleural mesothelioma. Patients were randomised to the tremelimumab (n = 382) or placebo (n = 189) arms. There was no difference in median overall survival time between these arms: 7.7 *vs.* and 7.3 months (HR = 0.92; 95% CI 0.76–1.12; p = 0.41). Grade 3 or higher adverse events occurred in 246 (65%) of 380 patients treated with tremelimumab and 91 (48%) of 189 patients who received placebo. Treatment-related events leading to death occurred in 36 patients (9%) of 380 *vs.* 12 (6%) of 189 patients in the other group [36].

In Poland, neither nivolumab in monotherapy nor pembrolizumab are registered for the treatment of pleural mesothelioma patients. In subsequent lines of treatment, chemotherapy remains standard of care. In the case of failure and in the 1st line of immunotherapy, two-drug chemotherapy should be included in the treatment, and in subsequent lines, exclusive symptomatic treatment or qualification for clinical trials should be considered. Drugs that have found use in pleural mesothelioma are also vinorelbine and gemcitabine [37, 38]. In 2016, a phase II trial evaluating the efficacy of vinorelbine in the second-line treatment of pleural mesothelioma opened in the United Kingdom. The study included 154 patients. Median PFS was 4.2 months in the vinorelbine arm and 2.8 months in the arm in which patients received symptomatic treatment only (HR = 0.59; 95% CI 0.41–0.85; p = 0.0017). Median OS was 9.3 and 9.1 months, respectively (HR = 0.79; 95% CI 0.53–1.17; p = 0.24) [39].

One study conducted by the European Organisation for Research and Treatment of Cancer Lung Cancer Cooperative Group (EORTC) was a phase II study of 27 patients with a diagnosis of pleural mesothelioma to evaluate the efficacy of gemcitabine. The median OS was 8 months and unequivocally demonstrated the activity of this chemotherapeutic agent against PM [40].

Pemetrexed in monotherapy has also been shown to be of therapeutic benefit in patients with pleural mesothelioma [41].

Summary

Antitumour systemic treatment can extend patients' lives often by many months or years. In pleural mesothelioma, a similar benefit has been achieved. The introduction of dual immunotherapy (nivolumab with ipilimumab) in the treatment of inoperable pleural mesothelioma prolonged OS by four months. Pleural mesothelioma has joined other cancers in which immunotherapy is already routinely used.

Surgical treatment remains the most effective method of radical treatment in mesothelioma. Further research is needed to best utilise the combination of resection with chemotherapy and radiotherapy in early-stage pleural mesothelioma patients.

In recent years, the development of anticancer treatment options has led to many cancers becoming chronic diseases. Pleural mesothelioma remains a disease with a poor prognosis with a relatively short survival time, but the achievements of recent years offer hope for further progress.

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Author contributions

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Conflict of interest

Authors declare no conflicts of interests.

Supplementary material

None.

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